Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-27 are pending in the application, with claims 1, 16, 18, 19, 22, 25, and 26 being the independent claims. Claims 1, 10, 15, 16, and 22 are sought to be amended, and new claims 24-27 are sought to be inserted. Support for the amendments and new claims 24-27 can be found in the original specification and claims as filed. These changes are believed to introduce no new matter, and their entry is respectfully requested. Specifically, X is $NR_9C(O)$ or $C(O)NR_9$ have been removed from claim 1 to further distinguish the claimed compounds from compounds allegedly disclosed in PCT published Appl. No. WO 99/62885. Applicants submit that no new matter has been introduced by this amendment since deletion of individual members of Markush expression does not constitute new matter. See, *In re Johnson and Farnham*, 194 U.S.P.Q. 187 (CCPA 1977). Claim 1 has also been amended by replacing "optionally substituted heteroaryl" in the definitions for R_1 with --heteroaryl optionally substituted with one or more groups independently selected from the group consisting of halo, . . . , and amino-- to further distinguish the claimed compounds from compounds allegedly disclosed in German published Appl. No. DE 1 936 760. Support for this amendment can be found at paragraph [0031] of the specification as originally filed. "R_4" in claim 10 has been amended to read --R_2--. Support for this amendment can be found at paragraph [0038], line 2, of the specification. Further, an obvious error in claim 15 has been amended by replacing "(vi)" with --(iv)--.

Support for new claim 24 can be found in claim 15 as originally filed. New claim 25 is supported by originally filed claims 1 and 7, and paragraph [0037] of the specification. New claim 26 is supported by paragraphs [0017], [0096], and [0097] of the specification.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

The present claims 1-23 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

According to the Examiner, the expressions "optionally substituted", "Het", "preferably", "can be", and "disorder responsive to" place no definite limits or boundaries on the claims. Applicants respectfully disagree. Applicants have amended claim 15 to remove the expression "preferably", and replaced the expression "can be" with --are-- in claims 16 and 22. With regard to the expression "optionally substituted" in claims 1, 2, 15, 16, 18, 19 and 22, Applicants respectfully submit that it would have been clear for a person skilled in the art at the time the application was filed that the expression "optionally substituted" means that a particular group is substituted or unsubstituted. See, *Ex parte Gordova*, 10 USPQ2d 1949 (B.P.A.I. 1988). Thus, Applicants respectfully submit that one skilled in the art would be able to ascertain the scope of protection defined by claims 1, 2, 15, 16, 18, 19, and 22 with regard to the expression "optionally substituted".

The expression "Het" is clearly defined in claims as a heteroaryl having a structure (i), (ii), (iii), or (iv) and, thus, would have been clear for a person skilled in the art. See, for example, claim 1, lines 6-7. Applicants respectfully submit that one skilled in the art would be able to ascertain the scope of protection defined by claims 1, 11-16, 18, 19, and 22 with regard to the expression "Het".

Applicants respectfully submit that the expression "disorder responsive to" in claim 18, which is the only claim containing this expression, would have been clear for a

person skilled in the art at the time the present application was filed. The specification describes in the beginning of paragraph [0091] that "[s]ince the compounds of Formula ***I*** are blockers of sodium (Na^+) channels, a number of diseases and conditions mediated by sodium ion influx can be treated employing these compounds." Further, paragraphs [0091], [0003] through [0007], and [0100] describe non-limiting examples of specific disorders responsive to the blockade of Na^+ channel activity. Applicants respectfully submit that one skilled in the art would be able to ascertain the scope of protection defined by claim 18 with regard to the expression "disorder responsive to".

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, of claims 1-23 are respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 19-21 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or which it is most nearly connected, to make and/or use the invention without undue experimentation. Applicants respectfully traverse this rejection.

The Examiner alleges as follows:

> [c]laim 19-21, are directed to "preventing or ameliorating" of neurodegenerative conditions, manic depression, neuropathic pain etc. to a mammal in need thereof. The claims refer to "preventing" of neuronal damage while all of the support in the specification enables "treating" and not "preventing". Because of the high level of unpredictability associated with the "preventing" of neuronal damage a greater amount of evidentiary support is needed in order to fully satisfy the requirement of 35 U.S.C. § 112, first paragraph. The applicant needs to provide sufficient guidance regarding "how to use" the invention properly.

(Office Action, page 3, line 4 from the bottom of the page through page 4, line 2).

Applicants respectfully disagree. First, the Examiner is incorrect in grouping the conditions claimed to be prevented in claims 19-21 as neuronal damages. Second, Applicants respectfully submit that preventing neuronal loss following global and focal ischemia, preventing neurodegenerative conditions, preventing pain, including neuropathic, surgical or chronic pain, or tinnitus, preventing manic depression, or preventing seizure activity as claimed in claims 19-21 are enabled. Na^+ channel blockers, such as BW619C89 and lifarizine have been shown to be neuroprotective in animal models of global and focal ischemia (see paragraph [0004] of the specification). Thus, sodium channel blockers have been shown to prevent neuronal loss following global and focal ischemia.

Riluzole, a sodium channel blocker approved by FDA for the treatment of ALS, has been shown to prolong survival in a subset of patients with ALS (see paragraph [0006], lines 1-4).

It would have been clear for a person skilled in the art at the time the application was filed that compounds having sodium channel blocking activity can be used for preventing the sensation of pain, including neuropathic pain, surgical pain or chronic pain. Further, based on the similarities between chronic pain and tinnitus, it has been proposed that tinnitus should be viewed as a form of chronic pain sensation. Lignocaine and carbamazepine, that are known to act by blocking or modulating sodium channel activity, have been shown to be efficacious in treating tinnitus (see paragraph [0006], lines 14-17 of the specification).

In addition to having been used for the treatment of manic depression (see paragraph [0006], lines 13-14), carbamazepine has been shown to be effective as a prophylactic treatment for manic depression (Denicoff, K. D., *et al.*, *J. Clin. Psychiatry* *55*:70-76 (1994)). Anticonvulsants, such as lamotrigine, phenytoin and carbamazepine, are known to act by blocking or modulating sodium channel activity (see paragraph [0003] of the specification), and are also described to prevent epileptic seizures (Catterall, W.A., *Trends Pharmacol. Sci.* *8*:57-65 (1987)). Further, Example 4 of the

specification shows that compounds of the present invention exhibit protection against maximal electroshock-induced seizures (MES).

Also, the specification provides suitable doses for disorders responsive to the blockade of sodium channels in mammal in paragraphs [0113] and [0114]. Specifically, doses for treatment or prevention of neuronal loss in global or focal ischemia are provided in paragraph [0114].

Furthermore, it would have been clear for a person skilled in the art at the time the invention was made how to identify those in need of such prevention of a disorder. Claim 19 clearly recites *that neuronal loss following* global and focal ischemia is prevented, i.e., global or focal ischemia have already been diagnosed. Further, Applicants respectfully submit that it would be clear for the skilled artisan, i.e., a medical doctor, to identify the people who would have a potential of becoming afflicted with neurodegenerative conditions, pain, including neuropathic pain, surgical pain and chronic pain, tinnitus, manic depression, and seizure activity based on the medical history of the patient and, thus, prevent, e.g., manic depression or neurodegenerative conditions by administering a Na^+ channel blocker of the present invention.

In summary, Applicants submit that the specification provides sufficient guidance as to how to use the invention as recited in claims 19-21.

Moreover, the Examiner alleges as follows:

> [i]t has not been shown in the specification that the "preventing" of such disorders is accepted in the art as being predictive of the utility alleged, especially when absent of pharmacological data (testing protocol). Merely stating that the instant compounds are useful for "preventing" against neuronal damage does not establish the usefulness of an invention absent art-recognized correlation between such tests and the ultimate use. Identifying substances as objects for further use testing (speculative utility) is insufficient to provide enabling disclosure. See Brenner v. Manson, 148 USPQ689 or In re Kirk, 153 USPQ 48.

(Office Action, page 4, lines 2-9).

Applicants respectfully disagree. It is submitted that the PTO must have adequate support for its challenge to the credibility of Applicants' statements as to utility. *In re Bundy*, 209 USPQ 48 (CCPA 1981). Further, "[o]nly after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility." *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Applicants respectfully submit that the Examiner fails to provide such adequate support.

Furthermore, the Examiner alleges at page 4, lines 9-12, of the Office Action that Applicants do not give sufficient direction or guidance in enabling these claims, and that the quantity of experimentation required to make and use the invention based on the content of the disclosure would therefore be undue because of the level of unpredictability associated with "preventing" of neuronal damage. Applicants respectfully disagree. In view of the above arguments, Applicants maintain that the specification teaches to one skilled in the art how to make and use the claimed invention without undue experimentation.

Reconsideration and withdrawal of the rejection of claims 19-21 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,
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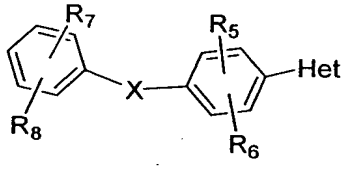
Version with markings to show changes made

New claims 24-27 have been inserted.

Claims 1, 10, 15, 16, and 22 have been amended as follows:

1. (Once Amended) A compound having the Formula *I*:

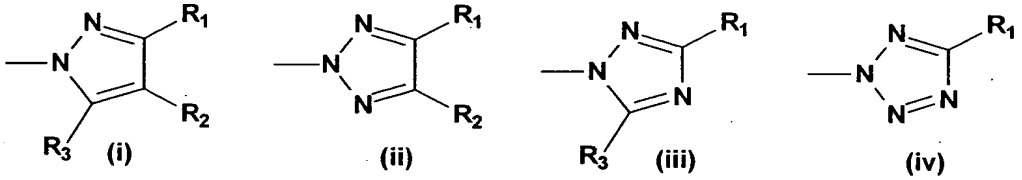


I

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

X is one of O, S, NR_9, or CH_2, [$NR_9C(O)$, or $C(O)NR_9$,] where R_9 is hydrogen or C_1-C_{10} alkyl;

Het is a heteroaryl selected from the group consisting of



R_1 is selected from the group consisting of hydrogen, optionally substituted alkyl, [optionally substituted] heteroaryl optionally substituted with one or more groups independently selected from the group consisting of halo, halo(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, hydroxy, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, aminocarbonyl, carbamoyloxy, C_{1-6} alkylsulfonylamino, C_{1-6} acyl and amino, $C(O)R_{10}$, $CH_2C(O)R_{10}$, $S(O)R_{10}$, and SO_2R_{10};

R_2 and R_3 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, cyano, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, aminosulfonyl,

alkylaminosulfonyl, and alkylsulfonyl;

R_5, R_6, R_7, and R_8 are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_{10} is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR_{11}, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, cycloalkyl, heterocycle, heteroaryl, aryl, aralkyl, arylalkenyl, arylalkynyl, and cycloalkylalkylamino;

R_{11} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

provided that:

1) when Het is (ii), and X is O, then R_{10} is not alkyl, aralkyl, aryl or OR_{11};
2) when Het is (i) or (ii), then X is not NR_9;
3) when Het is (iii), then X is not CH_2; and
4) when Het is (iii), and X is O, then R_{10} is not OR_{11}.

10. (Once Amended) A compound of claim 9, wherein:

R_5 and R_6 are each hydrogen;

R_3 and [R_4] $\underline{R_2}$ are both H; and

R_7 and R_8 are selected from the group consisting of hydrogen, halo, halo(C_1-C_6)alkyl, C_1-C_6 alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, alkoxy(C_1-C_6)alkyl, nitro, amino, C_1-C_6 acylamino, amide, hydroxy, thiol, C_1-C_6 acyloxy, C_1-C_6 alkoxy, carboxy, carbonylamido and C_1-C_6 alkylthiol.

15. (Once Amended) A compound of claim 1, wherein:

Het is (i), (ii), (iii) or [(vi)] $\underline{(iv)}$;

R_1 is $C(O)R_{10}$, $CH_2C(O)R_{10}$, or SO_2R_{10};

X is O or S;

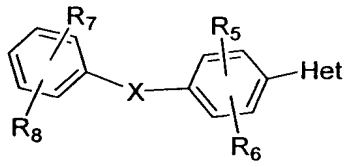
R_{10} is amino, optionally substituted C_1-C_6 alkyl, or a heterocycle selected from the group consisting of N-morpholinyl, N-pyrrolidinyl and N-piperazinyl;

R_2, and R_3 are independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylthio or C_1-C_6 alkylsulfinyl,

R_5 and R_6 are as defined [above and are preferably hydrogen] in claim 1, and

R_7 and R_8 are independently selected from the group consisting of hydrogen, halo, halo(C_1-C_6)alkyl, C_1-C_6 alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, alkoxy(C_1-C_6)alkyl, nitro, amino, C_1-C_6 acylamino, amide, hydroxy, thiol, C_1-C_6 acyloxy, C_1-C_6 alkoxy, carboxy, carbonylamido and C_1-C_6 alkylthiol.

16. (Once Amended) A compound of Formula *I*:



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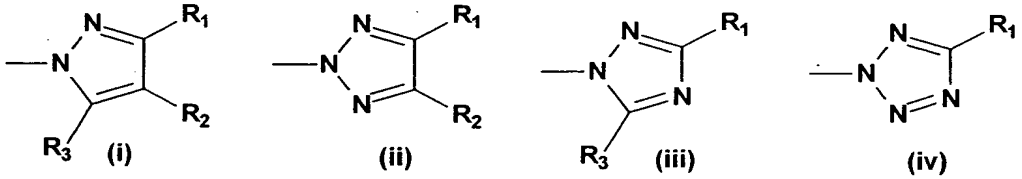
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

X is O or S;

Het is a heteroaryl selected from the group consisting of



R_1 is $C(O)R_{10}$, $CH_2C(O)R_{10}$, or SO_2R_{10} wherein R_{10} is amino, alkyl, N-morpholinyl, N-pyrrolidinyl or N-piperazinyl, all of which [can be] are optionally substituted;

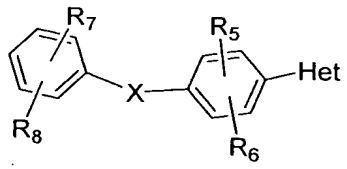
R_2 and R_3 are independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylthio or C_1-C_6 alkylsulfinyl;

R_5, R_6, R_7 and R_8 are independently selected from the group consisting of hydrogen, halo, halo(C_1-C_6)alkyl, C_1-C_6 alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, alkoxy(C_1-C_6)alkyl, nitro, amino, C_1-C_6 acylamino, amide, hydroxy, thiol, C_1-C_6 acyloxy, C_1-C_6 alkoxy, carboxy, carbonylamido and C_1-C_6 alkylthiol;

provided that:

1) when Het is (ii), and X is O, then R_{10} is not alkyl, aralkyl, aryl or OR_{11}; and
2) when Het is (iii), and X is O, then R_{10} is not OR_{11}.

22. (Once Amended) A compound of Formula ***I***:



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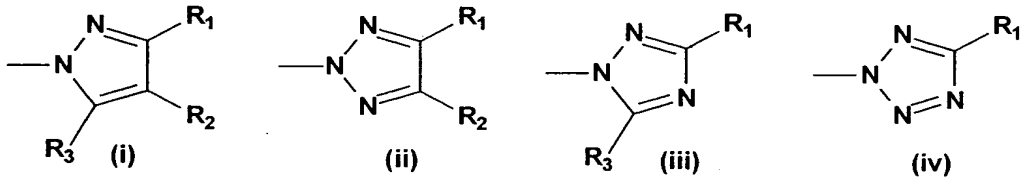
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

X is O or S;

Het is a heteroaryl selected from the group consisting of



R_1 is $C(O)R_{10}$, wherein R_{10} is amino, N-morpholinyl, N-pyrrolidinyl or N-piperazinyl, all of which [can be] <u>are</u> optionally substituted

R_2 and R_3 are independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylthio or C_1-C_6 alkylsulfinyl;

R_5, R_6, R_7 and R_8 are independently selected from the group consisting of hydrogen, halo, halo(C_1-C_6)alkyl, C_1-C_6 alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, alkoxy(C_1-C_6)alkyl, nitro, amino, C_1-C_6 acylamino, amide, hydroxy, thiol, C_1-C_6 acyloxy, C_1-C_6 alkoxy, carboxy, carbonylamido and C_1-C_6 alkylthiol.